UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION
1200 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20460-0001

MEMORANDUM

DATE: July 14, 2016

SUBJECT: **Chlormequat chloride:** Summary of Hazard and Science Policy Council (HASPOC) Meeting on April 14, 2016: Recommendation on the Need for an Immunotoxicity Study.

PC Code: 018101
Decision No.: NA
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0057428
MRID No.: NA

DP Barcode: NA
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 999-81-5
40 CFR: NA

FROM: Vincent Chen, Executive Secretary
HASPOC
Health Effects Division (7509P)

THROUGH: Jeff Dawson, Co-Chair
Jonathan Leshin, Co-Chair
HASPOC
Health Effects Division (7509P)

TO: Evisabel Craig, PhD, DABT, Toxicologist
Bridgett Bobowiec, Risk Assessor
Donna Davis, Branch Chief
Risk Assessment Branch VI (RAB6)
Health Effects Division (7509P)

MEETING ATTENDEES

HASPOC Members: Jonathan Chen, Jaime D'Agostino, Anwar Dunbar, Kelly Lowe, Ray Kent, John Kough, Elizabeth Mendez, and Michael Metzger

Presenter: Bridgett Bobowiec and Evisabel Craig

Other Attendees: Joey Bever, Sarah Dobreniecki, Sheila Piper, and Christopher Schlosser

I. PURPOSE OF MEETING

A registration review scoping document is currently being prepared for chlormequat chloride. The toxicology database for chlormequat chloride is complete except for an immunotoxicity study that is required in accordance with the current 40 CFR Part 158.500 Toxicology Data Requirements. The Hazard and Science Policy Council (HASPOC) met on April 14, 2016 to determine if the required study is necessary to support the registration review for chlormequat chloride.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATION

a. Use and Exposure Profile

Chlormequat chloride [(2-chloroethyl) trimethylammonium chloride] is a plant growth regulator (PGR) that belongs to the quaternary ammonium class of chemicals. Chlormequat chloride works through inhibition of gibberellin hormones. The end-use products are formulated as liquids (soluble concentrate/liquid) and contain 11.8% of the active ingredient, chlormequat chloride. The product is applied to ornamental plants grown in greenhouses, nurseries, and shadehouses. Use is restricted to containerized ornamentals. Chlormequat chloride applications are made using several types of application equipment – including groundboom sprayers, low pressure handwands, backpack sprayers, and high pressure handwands. Based on the number of seasonal applications indicated on product labels and information provided by the registrant, non-dietary exposures are expected to be short- and intermediate-term in duration. There are no current residential or food uses associated with chlormequat chloride, but the registrant anticipates the submission of a food-use registration application in the near future.

b. Toxicity Profile

Decreases in body weight and neurotoxicity are the most common effects observed in the chlormequat toxicity database across species and at different durations. There was no quantitative or qualitative susceptibility observed in the offspring compared to the adult animals in the rat and rabbit developmental studies or in the two-generation reproduction study (rat). Chlormequat is classified as "not likely to be a carcinogen" based on lack of evidence of carcinogenicity in rat and mouse studies. No evidence of mutagenicity or Immunotoxicity was reported in the chlormequat database.

In the most recent risk assessment (D. Wilbur, 2007), a prenatal developmental toxicity study in rats was used for establishing the acute oral reference dose (aRfD) of 0.9 mg/kg/day. The oral NOAEL was 90 mg/kg/day and the LOAEL was 180 mg/kg/day is based on tremors and ataxia in dams after a single oral dose on gestation day 6 (GD 6). The chronic RfD (cRfD) of 0.05 mg/kg/day is derived from a NOAEL of 5 mg/kg/day from the dog chronic toxicity study (MRID 46715201), with a LOAEL of 10 mg/kg/day, based on salivation (after 1 week, both sexes), vomiting (females) and diarrhea (males).

III. STUDY WAIVER REQUESTS

a. **Immunotoxicity Study**

1. **Indicators for potential immunotoxicity:** No indicators of immunotoxicity were identified in the chlormequat chloride toxicity database.

Parameter	Findings
Hematology Indicators (WBC changes)	No evidence
Clinical Chemistry Indicators (A/G Ratio)	No evidence
Organ Weight Indicators (Spleen, Thymus)	No evidence
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	No evidence
Toxicity Profile (Target Organ)	Nervous system

2. **Evidence for immunotoxicity from SAR chemicals – Retrospective analysis:** According to HED's ISTEP database, there are two structurally similar chemicals to chlormequat chloride: diquat and ecolyst. An available mouse immunotoxicity study for diquat did not identify signs of immunotoxicity up to the highest dose tested (81 mg/kg/day). No immunotoxicity study is available for ecolyst, but no signs of immunotoxicity were reported in the ecolyst database.

3. **Risk assessment considerations:** The most sensitive endpoints currently used to assess exposure and risk are based on body weight changes and signs of neurotoxicity and are considered protective of any potential immunotoxicity (D336712, 2007).

IV. HASPOC CONCLUSIONS

Based on a WOE approach, considering all the available chlormequat chloride hazard and exposure data, the HASPOC recommends that an immunotoxicity study is not required at this time. This approach included the following considerations: (1) the toxicology database for chlormequat chloride does not suggest that the immune system is the primary target organ; (2) for other registered quaternary ammonium herbicides, the immune system is not the primary target organ and these chemicals did not elicit immunotoxic effects in guideline studies; and (3) an immunotoxicity study is not likely to identify a lower POD or a more sensitive endpoint for risk assessment.